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(54) Title: USE OF AN ANGIOTENSIN II TYPE 1 RECEPTOR ANTAGONIST IN THE MANUFACTURE OF A MEDICAMENT FOR THE TREATMENT OF CARDIOVASCULAR COMPLICATIONS

(57) Abstract: The present invention relates to the use of an angiotensin II type 1 receptor antagonist in the manufacture of a medicament for the prophylactic and/or therapeutic treatment of cardiovascular complications encountered in a patient in need of dialysis. The invention further relates to a method for prophylactic and/or therapeutic treatment of cardiovascular complications encountered in a patient in need of dialysis, comprising administering to the patient a therapeutically effective amount of an angiotensin II type 1 receptor antagonist.

USE OF AN ANGIOTENSIN II TYPE 1 RECEPTOR ANTAGONIST IN THE MANUFACTURE OF A MEDICAMENT FOR THE TREATMENT OF CARDIOVASCULAR COMPLICATIONS

FIELD OF THE INVENTION

The present invention relates to the use of an angiotensin II type 1 receptor antagonist in the manufacture of a medicament for the prophylactic and/or therapeutic treatment of cardiovascular complications encountered in a patient in need of dialysis. The invention further relates to a method for prophylactic and/or therapeutic treatment of cardiovascular complications encountered in a patient in need of dialysis, comprising administering to the patient a therapeutically effective amount of an angiotensin II type 1 receptor antagonist.

BACKGROUND OF THE INVENTION

Compounds that interfere with the renin-angiotensin system (RAS) are well-known in the art and are used to treat cardiovascular diseases, particularly arterial hypertension and cardiac failure. Principally, the RAS can be interfered with by inhibition of the enzymes synthesizing angiotensins or by blocking receptors at the effector sites. Available today are renin-antagonists, inhibitors of the angiotensin converting enzyme (ACE) and angiotensin II (AT II) receptor antagonists.

Angiotensin II type 1 receptor antagonists for which the present invention has found a new medical use are thus known in the art. However, nothing has been disclosed in connection with their potential effects in dialysis and more particularly hemodialysis.

Hemodialysis is a process for removing waste products and toxins from the blood of patients with renal malfunction or failure. Blood is removed from, and returned to, circulation, either through an artificial arterio-venous fistula or a temporary or permanent internal catheter, and passes through an "artificial kidney", or dialyzer.

Dialyzers vary in design and performance, but all include a dialysis membrane and a dialys-ing solution. In dialysis, toxins are removed by diffusion through the dialysis membrane, thus essentially restoring blood to its normal state. The process, however, has to be repeated at regular intervals, e.g. two to three times per week for four to six hours per session.

Patients subject to hemodialysis are currently treated in hospitals, due to the high cost and the complexity of the dialysis equipment. For patients in hemodialysis, the prognosis has been improved over the last decades. One reason is improved dialysis equipment and procedures. Thus, new and more effective dialysis filters have been developed to allow more efficient dialysis with improved clearance of toxic substances. Another alternative to more effective dialysis filters is to use more frequent dialysis sessions. Currently, most patients are offered four hour dialysis sessions three times per week, all year round. Trials comparing frequency of dialysis sessions indicate that the survival rate will be improved if patients can accept such dialysis sessions four times per week. Understandably, all patients cannot manage such frequent hospital visits.

Mortality among patients treated with hemodialysis due to end-stage renal insufficiency is very high. A large proportion of these deaths, approximately 50 to 65%, are reported to be caused by cardiovascular complications. For example, in a Danish national registry report from 1996, cardiac causes of death and stroke were noted in 51% and 11% of the patients, respectively. Data from the European Registry, the so-called ERA-EDTA registry show that more than 44% of the hemodialyzed patients die of cardiac events, 33% of which from myocardial infarction and 23% from sudden death.

In most patients subject to hemodialysis, the non-functioning kidneys are left intact. The main reason for this, is that it involves major surgery to remove them.

It is likely that non-functioning kidneys excrete a number of kidney-derived toxic substances which increase the risk of cardiovascular complications in these patients.

Further support of this hypothesis, is that patients in hemodialysis who have had their kidneys removed seem to exhibit a reduced risk for such adverse effects on the cardiovascular system. Consequently, such patients run a reduced risk of cardiovascular complications.

Improved medical treatment of patients in hemodialysis has also resulted in prolonged survival as well as a reduced risk and duration of hospitalization due to complications. Although few large scale trials have been performed, treatment of cardiovascular diseases, such as hypertension, have improved. The infections which frequently occur in dialysis patients can nowadays be better managed. Furthermore, the restoration of red blood cell formation using e.g. recombinant erythropoetin (EPO) has improved the survival rate and increased quality of life (QoL).

Despite these medical advances, the prognosis for patients in dialysis, and especially chronic hemodialysis, remains poor. A medical treatment that can significantly reduce mortality and morbidity due to cardiovascular complications would clearly be a major therapeutic advance.

SUMMARY OF THE INVENTION

The inventors of the present invention, have surprisingly found that the cardiovascular complications, such as mortality and morbidity, encountered in patients subject to dialysis, especially chronic hemodialysis, due to end-stage renal disease can be reduced by using an angiotensin II type 1 receptor antagonist during and/or between the dialysis sessions. Thus, use of an angiotensin II type 1 receptor antagonist can significantly reduce mortality due to cardiovascular diseases and reduce the number and duration of hospitalizations due to cardiovascular complications.

The present invention thus relates to a new method of preventing and/or treating cardiovascular diseases and complications by pharmacological interference with the renin-angiotensin system (RAS) using an angiotensin II type 1 receptor antagonist.

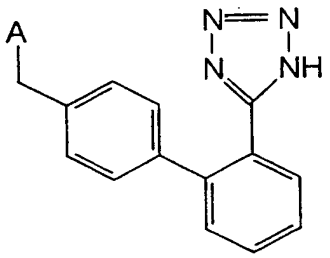
Angiotensin II type 1 receptor antagonists are conventionally used for preventing and/or treating hypertension. The present invention, however, is directed to prevention and/or treatment of cardiovascular complications other than hypertension, e.g. mortality and morbidity as stated above. Further cardiovascular complications which may be prevented and/or treated with the present invention include, without limitation myocardial infarction (MI), stroke, vascular access dysfunction and amputations.

In one embodiment, the present invention relates to use of an angiotensin II type 1 receptor antagonist in the manufacture of a medicament for the prophylactic and/or therapeutic treatment of cardiovascular complications encountered during or between dialysis of a patient in need of such dialysis.

A further embodiment of the invention provides a method for prophylactic and/or therapeutic treatment of cardiovascular complications encountered in dialysis of a patient, comprising administering to a patient in need of such dialysis a therapeutically effective amount of an angiotensin II type 1 receptor antagonist.

DETAILED DESCRIPTION OF THE INVENTION

In preferred embodiments of the present invention use is made of an angiotensin II type 1 receptor antagonist of the general formula I:



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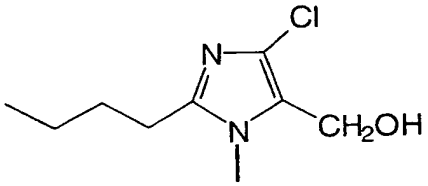

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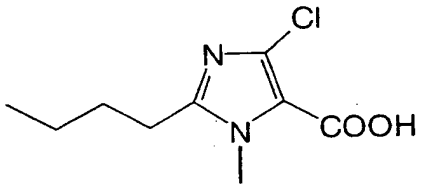

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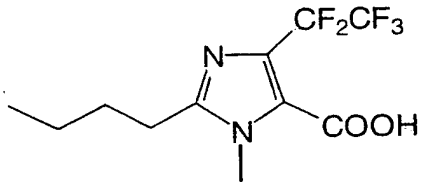

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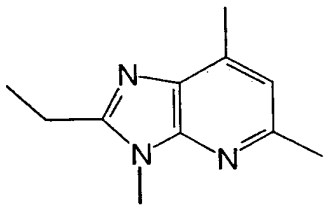

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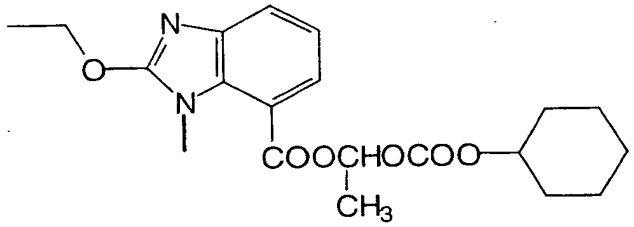

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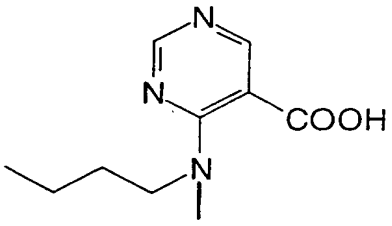

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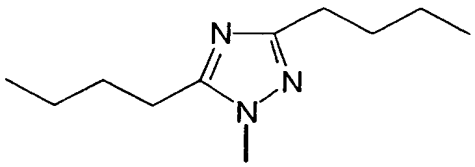

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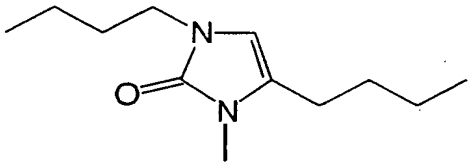

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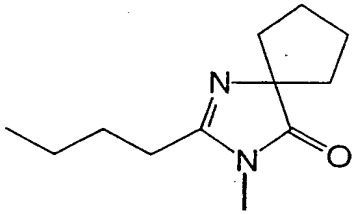

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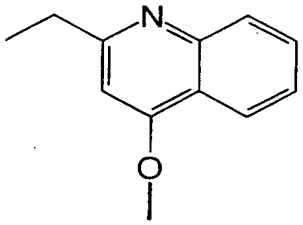

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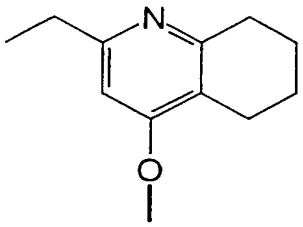

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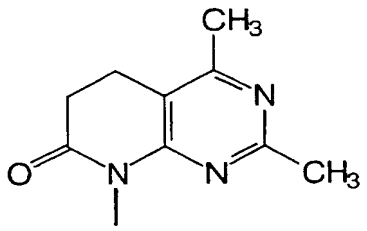

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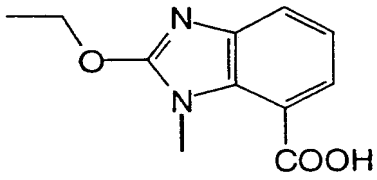

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The compound of the general formula I wherein A is the I:1 moiety has the generic name losartan and is known from European Patent No. EP 0 253 310 B1 to du Pont.

The compound of the general formula I wherein A is the I:5 moiety has the generic name candesartan cilexetil and is known from European Patent No. 459 136 B1 and US 5,196,444 to Takeda Chemical Industries.

The compound of the general formula I wherein A is the I:9 moiety has the generic name irbesartan.

The compound of the general formula I wherein A is the I:13 moiety has the generic name candesartan and is known from European Patent No. 459 136 B1 and US 5,703,110 to Takeda Chemical Industries.

In preferred embodiments of the present invention, use is made of a compound of the general formula I wherein A I:5 (candesartan cilexetil) or A is I:13 (candesartan). Candesartan cilexetil is currently manufactured and sold world-wide e.g. under the trade names Atacand®, Amias® and Blopress®.

When the angiotensin II type 1 receptor antagonists used in the present invention have several asymetric carbon atoms, they can consequently exist in several stereochemical forms. The present invention includes the mixture of isomers as well as the individual stereoisomers. The present invention further includes geometrical isomers, rotational isomers, enantiomers, racemates and diastereomers.

Where applicable, the angiotensin II type 1 receptor antagonists may be used in neutral form, e.g. as a carboxylic acid, or in the form of a salt, preferably a pharmaceutically acceptable salt such as the sodium, potassium, ammonium, calcium or magnesium salt of the compound at issue. Where applicable the compounds listed above can be used in hydrolyzable ester form.

In the present invention, angiotensin II type 1 receptor antagonists include all prodrugs thereof, whether active or inactive *in vitro*. Thus, although such protected derivatives may not possess pharmacological activity *per se*, they may be administered e.g. parenterally or orally, and thereafter metabolized *in vivo* to form pharmacologically active angiotensin II type 1 receptor antagonists.

The angiotensin II type 1 receptor antagonists may be used prior to and/or during dialysis.

In the present invention, dialysis includes hemodialysis and peritoneal dialysis. The present invention is preferably used for treating patients in hemodialysis, especially in chronic hemodialysis.

In the present invention, treatment of patients "in need of (treatment by) dialysis" relates to prophylactic and/or therapeutic treatment of patients suffering from renal complications and/or renal failure, including chronic and/or acute renal failure. The term also includes the prophylactic and/or therapeutic treatment of patients with intoxication by compounds that may give rise to organ damage, severe metabolic disturbances and/or death.

The present invention also relates to use of an angiotensin II type 1 receptor antagonist in the manufacture of a medicament for the prophylactic and/or therapeutic treatment of cardiovascular complications encountered in dialysis of a patient in need of such dialysis, wherein the angiotensin II type 1 receptor antagonist is provided in the dialysing solution.

The angiotensin II type 1 receptor antagonists may be provided as part of a dialysing solution ready for use in dialysis or provided as part of a dialysis concentrate, which concentrate is to be diluted before being used as part of a dialysing solution.

Normally, however, the angiotensin II type 1 receptor antagonists are administered by the oral or parenteral route, e.g. by intravenous, subcutaneous or intramuscular administration. Other possible routes of administration include rectal and transdermal administration. The formulation may be given in dosage unit form, especially as tablets or capsules.

According to a further aspect of the invention, there is provided a pharmaceutical formulation for use in the prophylactic and/or therapeutic treatment of cardiovascular complications encountered in dialysis of a patient in need of such dialysis, comprising an angiotensin II type 1 receptor antagonist as active substance in optional admixture with pharmaceutically acceptable adjuvants, diluents and/or carriers.

The adjuvants, diluents and/or carriers used in the pharmaceutical formulations of the present invention, may be conventional ones well known to the person skilled in the art. Examples of such adjuvants, diluents and/or carriers include substances used as binders, lubricants, fillers, disintegrants, pH regulants and thickeners as well as substances included for providing isotonic solutions.

The dose of the angiotensin II type 1 receptor antagonist and in particular a compound according to formula I to be administered in prophylaxis and/or treatment of dialysis patients will depend primarily upon the angiotensin II type 1 receptor antagonists which is used, the route of administration, the severity of the disease to be treated and the status of

the patient. The daily dose, especially at oral, rectal as well as parenteral administration, can be in the range of from about 0.01 mg to about 1000 mg per day of active substance, suitably from 0.1 mg to 500 mg per day of active substance, particularly from 1 mg to 100 mg per day of active substance. In preferred embodiments where candesartan and derivatives thereof are used, including candesartan cilexetil, the dosage range at oral, rectal as well as parenteral administration can be in the range of from about 0.1 mg to about 50 mg per day, particularly from 0.2 mg to 25 mg per day calculated as candesartan.

EXAMPLE

The invention is illustrated by reference to the following Example which is not intended to limit the invention in any way.

EXAMPLE 1

Pilot study design

A pilot study in which the effects of the angiotensin II type 1 receptor antagonist candesartan cilexetil (Atacand®) is compared to that of placebo, will be carried out to explore the feasability of giving candesartan cilexetil to patients in need of hemodialysis to reduce cardiovascular complications.

The pilot study will be double-blind placebo controlled performed in patients receiving hemodilaysis. The persons will be 2:1 randomized to treatment with active or inactive medication, such that 14 persons will receive candesartan cilexetil (Atacand®) and 7 persons will receive placebo. The dose titration will be 4 to 8 to 16 based on tolerance, two weeks allowed per dose.

The study will provide preliminary data on the feasibility of administering candesartan cilexetil to hemodialysis patients. It may also provide preliminary data on useful concentrations of candesartan cilexetil.

EXAMPLE 2

Large-scale study design

A large-scale clinical trial in which the effects of the angiotensin II type 1 receptor antagonist candesartan cilexetil (Atacand®) is compared to that of placebo, will be carried out to explore the usefulness of giving candesartan cilexetil to patients in need of hemo-dialysis to reduce cardiovascular complications.

Treatments will be given to patients undergoing chronic hemodialysis treatment due to renal insufficiency. Patients will be recruited from hospitals with special dialysis departments. The patients will be randomized to double-blind treatment with active or inactive medication, i.e. candesartan cilexetil or placebo.

The study will also provide more detailed data on the feasibility of administering candesartan cilexetil to hemodialysis patients. It may also provide data on useful concentrations of candesartan cilexetil.

CLAIMS

1. Use of an angiotensin II type 1 receptor antagonist in the manufacture of a medicament for the preventive and/or therapeutic treatment of cardiovascular complications encountered in a patient in need of dialysis.

2. Use according to claim 1, wherein the angiotensin II type 1 receptor antagonist is administered by the oral or parenteral route.

3. Use according to claim 1, wherein the angiotensin II type 1 receptor antagonist is administered by the rectal or transdermal route.

4. Use according to any one of claims 1 to 3, wherein the angiotensin II type 1 receptor antagonist is administered in dosage unit form, suitably as tablets or capsules.

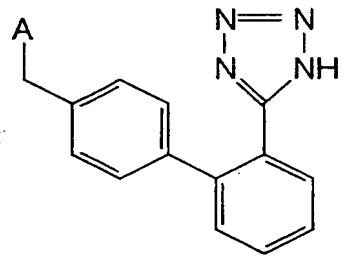
5. Use according to claim 1, wherein the angiotensin II type 1 receptor antagonist is provided in the dialysing solution.

6. Use according to any previous claim, wherein the dialysis is hemodialysis.

7. Use according to any previous claim, wherein the cardiovascular complication is selected from the group consisting of mortality and morbidity.

8. Use according to any previous claim, wherein the cardiovascular complication is selected from the group consisting of myocardial infarction (MI), stroke, vascular access dysfunction and amputations.

9. Use according to any previous claim, wherein the angiotensin II type 1 receptor antagonist is a compound of the general formula I



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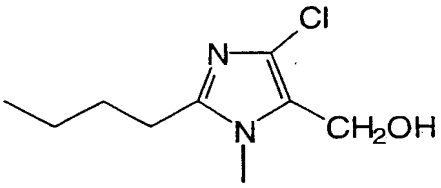

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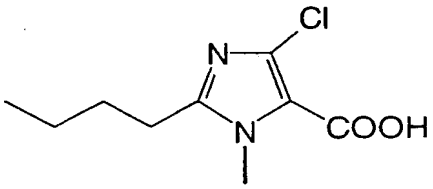

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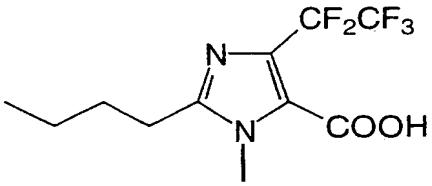

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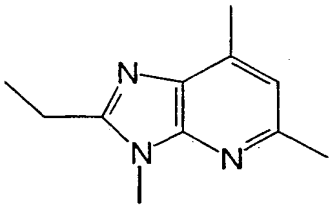

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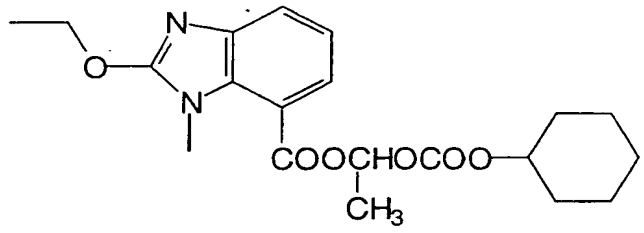

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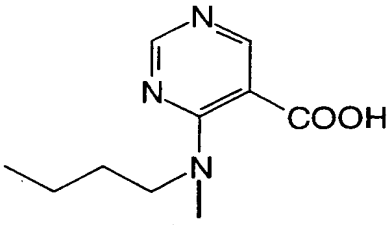

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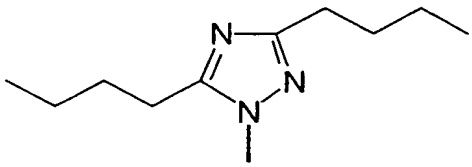

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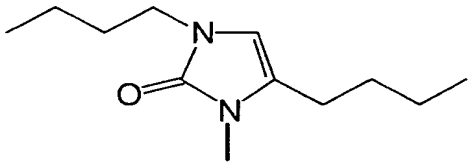

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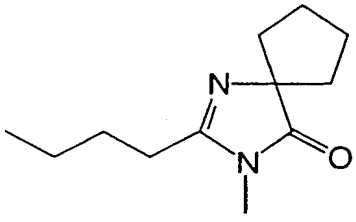

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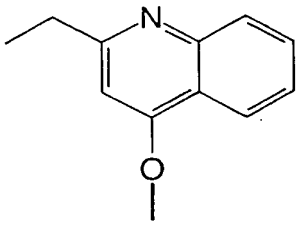

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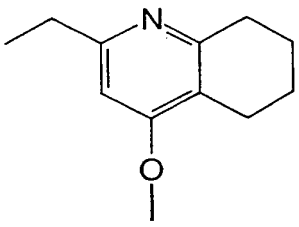

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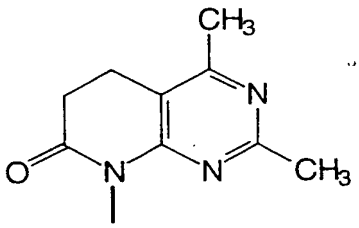
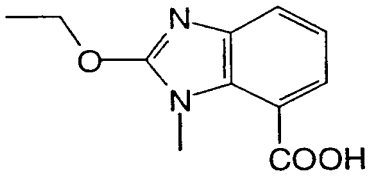


I:12

and



I:13

pharmaceutically acceptable salts and stereochemical isomers of any of these.

10. Use according to claim 9 of a compound of the general formula I wherein A is I:5.

11. Use according to claim 9 of a compound of the general formula I wherein A is I:13.

12. A pharmaceutical formulation for use in the preventive and/or therapeutic treatment of cardiovascular complications encountered in a patient in need of dialysis, comprising an

angiotensin II type 1 receptor antagonist as active substance in optional admixture with pharmaceutically acceptable adjuvants, diluents and/or carriers.

13. The pharmaceutical formulation according to claim 12, wherein the angiotensin II type 1 receptor antagonist is a compound as defined in claim 9.

14. The pharmaceutical formulation according to claim 13, wherein the angiotensin II type 1 receptor antagonist is a compound as defined in claim 10 or 11.

15. The pharmaceutical formulation according to anyone of claims 7 to 9 in dosage unit form, suitably as tablets or capsules.

16. The pharmaceutical formulation according to any one of claims 12 to 15, wherein the daily dose lies in the range of from about 0.01 mg to about 1000 mg of active substance, preferably in the range of from 1 mg to 100 mg of active substance.

17. The pharmaceutical formulation according to claim 16, wherein the daily dose lies in the range of from about 0.1 mg to about 50 mg calculated as candesartan, preferably in the range of from 0.2 mg to 25 mg calculated as candesartan.

18. A method for preventive and/or therapeutic treatment of cardiovascular complications encountered in a patient in need of dialysis, comprising administering to such a patient a therapeutically effective amount of an angiotensin II type 1 receptor antagonist.

19. The method according to claim 18, wherein the angiotensin II type 1 receptor antagonist is administered by the oral or parenteral route.

20. The method according to claim 18, wherein the angiotensin II type 1 receptor antagonist is administered by the rectal or transdermal route.

21. The method according to any one of claims 18 to 20, wherein the angiotensin II type 1 receptor antagonist is administered in dosage unit form, suitably as tablets or capsules.

22. The method according to claim 18, wherein the angiotensin II type 1 receptor antagonist is provided in the dialysing solution.

23. The method according to any one of claims 18 to 22, wherein the dialysis is hemodialysis.

24. The method according to any one of claims 18 to 23, wherein the cardiovascular complication is selected from the group consisting of mortality and morbidity.

25. The method according to any one of claims 18 to 23, wherein the cardiovascular complication is selected from the group consisting of myocardial infarction (MI), stroke, vascular access dysfunction and amputations.

26. The method according to any one of claims 18 to 25, wherein the angiotensin II type 1 receptor antagonist is a compound as defined in claim 9.

27. The method according to claim 26, wherein the angiotensin II type 1 receptor antagonist is a compound as defined in claim 10 or 11.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 00/01444

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: A61K 31/41, A61P 9/10
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 9830216 A1 (MERCK & CO., INC.), 16 July 1998 (16.07.98) --	1-27
Y	KIDNEY INTERNATIONAL, Volume 54, No 68, 1998, Ramon Saracho et al, "Evaluation of the Losartan in Hemodialysis (ELHE) Study", page S-125 - page S-129 --	1-27
A	MED SCI MONIT, Volume 4, No 6, 1998, Zofia Wankowicz, "Cardiovascular agents in renal diseases" page 1104 - page 1110 --	1-27

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
2 November 2000	08 -11- 2000
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Carolina Gómez Lagerlöf/ELY Telephone No. +46 8 782 25 00

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 00/01444

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 9713513 A1 (NOVARTIS AG), 17 April 1997 (17.04.97), page 12 - page 13 -- --------	12-17

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE00/01444

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 18-27
because they relate to subject matter not required to be searched by this Authority, namely:

See extra sheet

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE00/01444

Claims 18-27 relate to methods of treatment of the human or animal body by surgery or by therapy/diagnostic methods practised on the human or animal body/ Rule. 39.1.(iv). Nevertheless, a search has been executed for these claims. The search has been based on the alleged effects of the compound(s)/composition(s).

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/SE 00/01444

WO	9830216	A1	16/07/98	AU	6021898 A	03/08/98
				CN	1249682 T	05/04/00
				EP	0966282 A	29/12/99
				GB	9704197 D	00/00/00
				JP	2000508347 T	04/07/00
				NO	993399 A	09/09/99
				ZA	9800163 A	10/07/98
WO	9713513	A1	17/04/97	AU	7213296 A	30/04/97
				BR	9611007 A	13/07/99
				CA	2232663 A	17/04/97
				EP	0853477 A	22/07/98
				JP	11513395 T	16/11/99
				US	6071931 A	06/06/00